Remarks

Claim 3 was amended to depend from claim 2. Claim 5 was amended to delete an extraneous percent sign.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

The Examiner alleges that the phrase "wherein R_1, R_2, R_3, and R_4 groups are..." in claim 3 lacks antecedent basis. Claim 3 was amended to depend from claim 2. Claim 3, as amended, is definite.

Rejections Under 35 U.S.C. § 102

Claims 1 and 8-13 were rejected under 35 U.S.C. § 102(b) as being unpatentable over U.S. Patent No. 6,075,056 to Quigley *et al.* ("Quigley"). Claims 1-3, 8-13, and 17 were rejected under 35 U.S.C. § 102(b) as anticipated by European Patent No. EP 1 159 956 to Burnett *et al.* ("Burnett"). Applicant respectfully traverses these rejections.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991).

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. (*see Scripps*, 18 USPQ2d at 1010).

In Air Products, the district court stated that "a prior art reference which contains a broad general disclosure requiring guessing, testing, speculation or 'picking and choosing' from an encyclopedic disclosure will not anticipate." 219 U.S.P.Q. at 231 (citing In re Arkley, 59 C.C.P.A. 804, 455 F.2d 586 (C.C.P.A. 1972)) (in order to anticipate, a piece of prior art "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference"); *In re Samour*, 571 F.2d 559, 562 (C.C.P.A. 1972); and *General Battery Corp. v. Gould, Inc.*, 545 F. Supp. 731, 740 (D. Del. 1982)). In *In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586 (Cust. Pat. App.1972), the Court of Customs and Patent Appeals held that the disclosures of the cited prior art must be sufficiently clear that a person of ordinary skill in the art would understand their full implication without resorting to speculation or guesswork. 455 F.2d at 587.

In General Battery, the court noted that a prior art reference "must contain within its four corners, adequate directions for the practice of the patent claim sought to be invalidated." 545 F. Supp. at 744 (internal quotation marks and citation omitted). "Unless all of the same elements are found in exactly the same situation and united in the same way to perform the identical function in a single prior art reference, there is no anticipation." Id. (internal quotation marks and citation

omitted). In analyzing the prior art reference cited by the defendant, the court found that the references which in combination allegedly anticipate the [patent-in-suit] are scattered throughout the work. One would have to pick and choose among various pages in Vinal to piece together a battery such as that claimed in the patents in suit. This process of selection would require some inventive skills to determine by simply reading Vinal's book that adding sodium sulfate in a conditioning amount to a moist battery would enhance the shelf life of that battery. The elements of the invention are not in the same location nor are adequate directions provided to manufacture the invention.

Analysis

Claim 3 was amended to depend from claim 2. Claim 5 was amended to delete an extraneous percent sign.

a. Quigley

Quigley describes topical formulations containing an antifungal agent and an anti-inflammatory steroid having a potency between 1 and 7 (i.e. of any strength, see col. 4 and 5) useful for treating fungal diseases (abstract). Suitable antifungal agents include benzylamine-containing antifungal agents, such as butenafine, and allylamine-containing antifungal agents, such as terbinafine, naftifine, and the like (col. 2, lines 4-6). Quigley discloses at columns 4 and 5 steroidal anti-inflammatories with potencies between 7 and 1. The potency is dependent not just on the structure of the molecule but also on the manner in which it is formulated (*see* the table at columns 4 and 5).

In contrast, applicant claims formulations containing a steroidal anti-inflammatory having a potency between 6 and 7 (i.e., low to low-medium potency steroidal anti-inflammatories). This selection of a narrow class of steroidal anti-inflammatories represents less than 20% of what Quigley says is effective. Applicant has presented data which clearly shows the criticality of the small set of steroidal anti-inflammatories specified in the claims and shows unexpected results across this small set (see, for example, the declaration of Dr. Jay Goldstein submitted with the Amendment and Response filed on June 1, 2006).

The purpose of Quigley is to provide compositions that have a synergistic effect in that antifungal activity in superior to that shown by the antifungal in the absence of the steroidal anti-inflammatory (col. 2, lines 16-19). Based on Quigley, one would expect to see lower efficacy for the formulations in Quigley when incorporating a low potency steroidal anti-inflammatory, and greater efficacy with stronger steroidal anti-inflammatories. This clearly teaches away from the claimed formulation which specifies that the steroidal anti-inflammatory is has a low to low-medium potency in order to avoid local side effects, such as skin atrophy, striae and hypopigmentation, and yet has excellent efficacy. This is neither disclosed by nor obvious from Quigley.

Quigley does not disclose or suggest a preference for low to low-medium potency steroids. One of ordinary skill would have to pick and choose among various compounds in various formulations to piece together the claimed formulations. The disclosure in Quigley is not sufficiently clear that a person of ordinary skill in the art would understand their full

implication without resorting to speculation or guesswork. Accordingly, claims 1 and 8-13 are novel over Quigley.

b. Burnett

Burnett describes anhydrous compositions for topical delivery of a medicament containing (a) a penetration enhancer/solvent selected from the group consisting of alcohol, propylene glycol, or a combination thereof; (b) a humectant/solvent selected from the group consisting of polyethylene glycol, glycerin, sorbitol, xylitol, or combinations thereof; an anhydrous vehicle; and (d) one or more medicaments (abstract). With respect to Example 1, Burnett alleges that the compositions delivered greater amounts of ketoconazole and desonide to the epidermis and dermis, but less to the receptor versus commercially known formulations such as NIZORAL® and DesOwen® (page 8, paragraph 0036). Burnett alleges that this may clinically translate to lower systemic absorption of the active agents, thereby lowering systemic active agent toxicity (page 8, paragraph 0036). Burnett also alleges that the compositions, after repeated application via a patch, did not induce contact dermal sensitization. Burnett, however, does not disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation. Accordingly, claims 1-3, 8-13, and 17 are novel over Burnett.

Rejections Under 35 U.S.C. § 103

Claims 2, 3, 7, and 14-17 were rejected under 35 U.S.C. § 103(a) as obvious over Quigley. Claims 4-6 were rejected under 35 U.S.C. § 103(a) as obvious over Burnett in view of U.S. Patent No. 5,219,877 to Shah *et al.* ("Shah"). Applicant respectfully traverses these rejections.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Supreme Court did not obviate the requirement for the references to provide some motivation to combine as applicants have done, with a reasonable expectation of success. Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

"The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Analysis

1. Quigley

(a) Determining the scope and contents of the prior art

Quigley is discussed above.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The Claimed Compositions

The claims define a topical antifungal composition containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone (i.e., a steroidal anti-inflammatory in the range of 6-7), and a carrier suitable for administration of the antifungal compound and the steroidal anti-inflammatory to the skin, wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects. Quigley's range is 0.001% to 5% steroidal anti-inflammatory (col. 5, line 58), again demonstrating that applicant has selected not only a small number of the steroidal antiinflammatories, but also a subset of the concentration range.

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, Quigley does not disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation as required by the claims. Further, Applicant has presented data which clearly shows the criticality of the small set of steroidal anti-inflammatories specified in the claims and shows unexpected results across this small set (*see* the declaration of Dr. Jay Goldstein submitted with the Amendment and Response filed on June 1, 2006). Accordingly, claims 2, 3, 7, and 11-14 are not obvious over Quigley.

2. Burnett in view of Shah

(a) Determining the scope and contents of the prior art

Burnett is discussed above. Shah describes a gel formulation comprising an imidazole antifungal agent, either by itself or in combination with a steroid anti-inflammatory agent. Id., column 3, lines 10-16. A litany of anti-inflammatory steroids is listed at column 3, line 54-column 4, line 2. A preference for mid-potency steroids is expressed at column 4, lines 3-16 of Shah. In fact, Shah discloses that mid-potency steroids are preferred in view of certain disadvantages of strong and low-potency steroids including undesirable side effects such as skin

atrophy, rebound phenomenon, and telangiectasia and the fact that low potency steroids may fail to provide fast relief from inflammatory symptoms (col. 4, lines 3-11).

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, neither Burnett nor Shah disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation as required by claim 1. Claims 4-6 depend from claim 1. In fact, Shah teaches away from the claimed compositions by disclosing that low to low-medium potency steroidal inflammatories cause undesirable side effects and are not effective in providing relief from inflammation. It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d

731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). Accordingly, claims 4-6 are not obvious over Burnett in view of Shah.

Allowance of claims 1-17 is respectfully solicited.

Respectfully submitted,

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